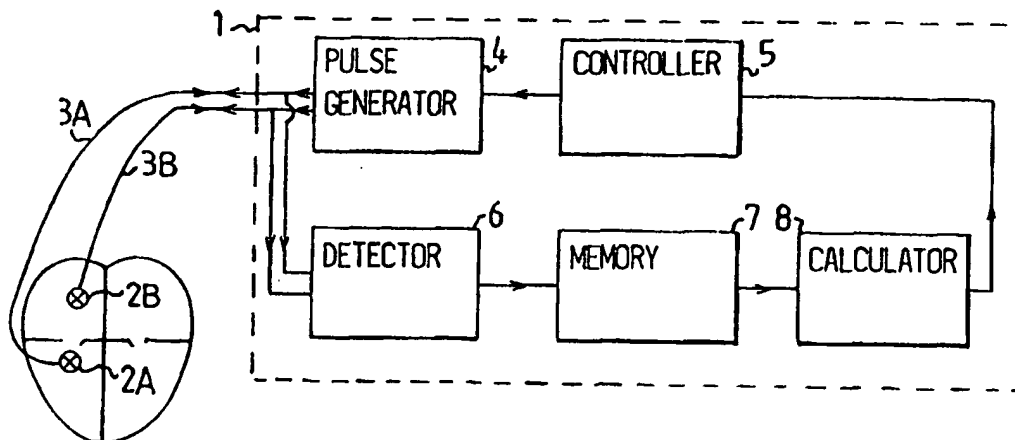




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61N 1/365</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/15319</p> <p>(43) International Publication Date: 16 April 1998 (16.04.98)</p>
<p>(21) International Application Number: PCT/EP97/05443</p> <p>(22) International Filing Date: 2 October 1997 (02.10.97)</p> <p>(30) Priority Data: 9603635-5 4 October 1996 (04.10.96) SE</p> <p>(71) Applicant (for all designated States except US): PACSETTER AB (SE/SE); S-175 84 Järfälla (SE).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): EKWALL, Christer (SE/SE); Årsvägen 4, S-163 57 Spånga (SE).</p> <p>(74) Agent: HARRISON, Michael, Charles; AlbiHns GmbH, Grasserstrasse 10, D-80339 München (DE).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: IMPLANTABLE DEVICE



(57) Abstract

The invention relates to an implantable stimulating device, e.g. heart pacemaker. The pacemaker (1) includes a means (6, 7, 8) for determining the variation in the spontaneous interval which corresponds to the length of the heartbeat cycle. The value of this variation may be used to control a pacemaker parameter such as pacing rate, and may be stored at regular time intervals to be available for monitoring.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Implantable device

5

Field of the Invention

The invention relates to implantable stimulator devices capable of providing electrical stimuli to the heart. The invention particularly relates to devices in which the
10 spontaneous rate variability is measured.

Background to the Invention

A heartbeat can be divided into two phases: the filling phase and the ejection phase.
15 These phases are shown diagrammatically in Figs. 1A-1E in which the two atria are indicated by A and the two ventricles by B with the heart valves indicated by C. In a first phase (Fig. 1A) the atria and ventricles are empty and blood arrives from the veins into the atria and when these are full the blood passes via the one-way heart valves into the ventricles. The atria then contract (see Fig. 1B) to pump blood from the atria into
20 the ventricles. The state is thus reached (see Fig. 1C) in which the atria are empty whilst the ventricles are full of blood. The ventricles then contract as shown in Fig. 1D to push the blood into the arteries. This is the heart beat. After the re-expansion of the ventricles the heart has arrived at the final stage (see Fig. 1E) has now returned to the same state as the initial stage of the heartbeat cycle.

25

As can be seen this cycle requires the heart to act in a coordinated sequential manner. In certain heart diseases this cycle is disturbed so that for instance the ventricle does not contract immediately after filling with blood but may contract too soon or too late. In order to treat this type of disorder, use is made of the fact that electrical pulses cause
30 muscles to contract. Pacemakers were therefore developed to provide electrical pulses at appropriate times to a diseased heart so that it would function in the same manner as

a healthy heart.

The basic function of a pacemaker is to provide pacing pulses for the muscles of the heart so that a diseased heart beats in a rhythm similar to that at which a healthy heart should beat. Where possible the pacemaker only provides a pacing pulse in a situation where the natural contraction of an atrium or ventricle does not take place at the expected appropriate point in time.

Although pacemakers have been used since about 1958 and are an undoubted success they are not always able to ensure that a diseased heart always functions in the same way as a healthy heart. One reason for this is that even for healthy individuals the heart does not always beat to the same rhythm, e.g. the natural heartbeat rate varies from individual to individual. Also for a single individual the rhythm may show variations from one beat to the next.

The invention is concerned with providing an improved implantable stimulator which overcomes these problems.

As mentioned above there may be variations in the time between heartbeats from one beat to the next. The time length for an unpaced heartbeat cycle, i.e. the length of time for the heart to complete a cycle, is known as the spontaneous interval. The time interval between the atrial contraction (Fig.1B) and the ventricular contraction (Fig. 1D) within a cycle is known as the AV-delay interval.

During clinical studies performed on animals, a variation in the spontaneous interval has been observed. This spontaneous interval variation (SIV) is not a result of workload, psychological or other influence. In a stable situation with no change of influence of environmental factors there may be a long spontaneous interval. This long interval is then followed by a short spontaneous interval and vice-versa. Corresponding variations in the AV-delay have been observed.

The range of variation is found to be different from one species to another, but it is always present. The interval variation in dogs has been found to be extreme compared to that of, for instance, sheep or pigs. Maximum variability is observed when the dog is awake but at rest and unstressed. On some occasions spontaneous intervals are found to vary from 412 ms (milliseconds) to 1505 ms between heartbeats under the same conditions. A corresponding variation in AV-delay is also observed (e.g. from 82 to 125 ms).

Fig. 2 shows an IEGM (intracardiac electrogram) for a dog at rest with a pacemaker operating in DDD mode at a rate of 30 per minute and an A-V delay of 250 ms. The variation in the spontaneous rate interval is clearly visible here.

It is known from literature that a low spontaneous interval variation may result from ischaemia, age and heart insufficiency. It is also known that the spontaneous interval variation is the result of Vagus (Parasympathetic) nerve activity whereas heart rate increase results from Sympathetic nerve system activity.

It appears that the extreme variation in dogs is in some way connected with dogs' ability to react instantaneously, i.e. to go from rest to maximum alert with minimal delay. Also the fact that interval variation is known to be reduced in humans by disease, age and disabilities leads to the conclusion that a high variability in the spontaneous interval indicates a high reserve of available capacity. High spontaneous interval variation in humans appears to be a sign of health whereas a low spontaneous interval variation is an indicator of heart insufficiency.

The variation in the spontaneous interval causes a problem with Bradycardia stimulation. In this case the interval before a pacing pulse is given is prolonged so as to allow for a spontaneous pulse. This - hysteresis - time is difficult to determine due to the spontaneous interval variation and if the hysteresis time is set too long for an unhealthy heart it can lead to a dangerously low heartbeat rate. Also, with a response rate pacemaker the maximum rate allowed may be too high for an unhealthy heart. The

present invention aims to overcome these problems.

According to the abstract of US-A-5 265 617 there is disclosed a device in which heart rate variability, i.e. the variability or the time between successive R-waves, together
5 with T-wave alternans are measured and are used together for diagnosing cardiac vulnerability to ventricular fibrillation.

EP-A-647 454 states that the changes in the difference between the sensor indicated pacing rate and the actual pacing rate can be used as a measure of the time rate of
10 change of the sensor rate. Variations in the intrinsic heart rate are not apparently measured.

According to the abstract of US-A- 5 466 245, in a DDD-type pacemaker the A-V delay is optimised by finding its value associated with the minimum heart rate variability
15 index. The natural heartbeat is not used.

This invention is based on the recognition that the spontaneous interval variation in the intrinsic heartbeat can be used to control parameters of a pacemaker or other device generating electrical stimuli or to monitor the heart.
20

These spontaneous intervals are present for almost all pacemaker patients, e.g. patients having so-called AV II-block have up to 75% spontaneous heartbeats.

By intrinsic heartbeat is meant the natural heartbeat without external influence which
25 could affect it in any part of its cycle.

The present invention relates to an implantable stimulator as set out in claim 1 and to an implantable monitoring device as set out in claim 6. Advantageous embodiments of the invention are set out in the dependent claims.
30

By way of example only, embodiments of an implantable stimulator, here in the form of

a heart pacemaker, and a monitoring device according to the invention will now be described with reference to the accompanying drawings, in which:

FIG. 1 shows the heart beat cycle in diagrammatic form.

5

FIG. 2 shows an IEGM of a dog at rest.

FIG. 3 shows a diagrammatic representation of a dual chamber pacemaker in accordance with a first embodiment of the invention.

10

FIG. 4 shows a diagrammatic representation of a dual chamber pacemaker in accordance with a second embodiment of the invention.

FIG. 5 shows a diagrammatic representation of a dual chamber pacemaker incorporating a third embodiment of the invention.

15

Referring to Fig. 3 the pacemaker is designated by 1. The electrodes 2A and 2B pace the ventricle and atrium respectively. Any suitable electrodes may be used for this purpose and may be unipolar or bipolar. Although shown in relationship to dual chamber pacing, the invention is equally applicable to single chamber pacing. The electrodes are connected by respective conduction leads 3A, 3B to a stimulation pulse generator 4.

20

The stimulation pulse generator 4 generates and sends electrical stimuli, here in the form of pulses, to the heart through the conduction leads 3A, 3B. The pulse generator may provide pulses whose characteristics, e.g. shape, amplitude etc. may be varied. The stimulation pulse generator is controlled by a programmable controller 5. The controller 5 controls the pulse generator in response to a program contained in its memory. The program used will depend upon the heart malfunction of the patient. The program may be changed in accordance with the instructions of the patient's doctor. This change may be effected by telemetry as is known per se. The controller includes a

30

clock as a timing reference for controlling the pulse generator.

Atrial and/or ventricular events are sensed by a detector 6. The time delay between two identical events on successive intrinsic heartbeat cycles corresponds to the spontaneous interval and is registered by the detector 6. In certain applications the detector registers the time delay between events on the same heartbeat cycle, e.g. the A-V delay. This time interval may be sensed in terms of a number of cycles of the pacemaker internal clock contained in the controller 5 or alternatively the detector may be provided with an independent clock.

10

The value of this time interval is sent to a memory 7. The memory 7 stores the values of a predetermined number of the latest recorded intervals, preferably at least five and typically eight. As a new interval value is received the oldest value is deleted from the memory. The interval values are accessed by the calculator 8 for establishing a signal representative of the spontaneous interval variation (SIV). This is done in this embodiment by identifying the largest and the smallest values in the set of interval values and calculating the difference in these two values. A signal representative of this difference is stored in the calculator and then sent to the controller 5. This signal is used by the controller 5 to vary a controlling parameter of the stimulation pulse generator. This parameter will vary according to the type of pacing being used.

20

The functions of the controller 5, memory 7 and calculator 8 may be provided by a suitably programmed microprocessor.

In an alternative embodiment the SIV is calculated using the variance of the stored values about their mean value as a statistical measure of the variability.

25

If the mean value is changing, e.g. due to the start or cessation of exercise, this may affect the mean value during the measurement and change the measurement of the SIV.

This change will not however be significant compared to the value of the SIV.

30

The above described embodiment is particularly useful where it is desired to control the Bradycardia stimulation insertion rate. In normal pacing a stimulation insertion rate is selected. In a simple form this means that pacemaker stimulation is inhibited as long as a spontaneous beat is sensed within the selected interval. In this simple form a problem arises from competition rhythm between pacemaker and sinus (spontaneous) rhythm. In the situation where the normal heart rate is reduced from a higher level to a lower level, a certain lower rate limit is allowed before the pacemaker takes over. However if even a small statistical variation in interval length is present, a point will be reached where the spontaneous interval is alternatingly shorter and longer than the pacemaker interval.

10

The resulting competitive rates are undesirable for some patients and can, in the presence of retrograde conduction, even result in the so-called Pacemaker Syndrome. This is a situation where atrial contraction is simultaneous to ventricular contraction. Pressure waves then propagate backwards in the venous system (Cannon waves) as a result of atrial contraction against a closed heart valve and reduces the arterial blood flow.

15

In order to reduce the effects of competitive rates, hysteresis may be introduced. Hysteresis means that the interval (escape interval) before a pacing pulse is given is prolonged by a certain amount. This has the effect that in normal sinus rhythm, the rate is allowed to drop to a lower spontaneous rate than the selected or programmed pacemaker rate.

20

The SIV is, as already indicated above, at its maximum at rest in the healthy heart. To be effective however the hysteresis time (interval prolongation) has to be long. This creates a problem as it means that the Bradycardia stimulation insertion rate will be correspondingly low. Hysteresis with a small interval prolongation is ineffective whereas with a long prolongation it may be inappropriate. As a result hysteresis is rarely used in practice in pacemaker treatments. As a result of the invention however it is now possible to use hysteresis in practice.

25

30

In accordance with this embodiment the SIV is evaluated and used by the pacemaker to control a parameter of the pacemaker, i.e. the hysteresis time. The hysteresis time is increased in accordance with the SIV so that for a healthy heart situation - high SIV - a high hysteresis time is maintained, allowing for the high natural SIV and avoiding competition rates. In the case of a heart disorder - low SIV - the hysteresis time is reduced and low pacing rates are thus avoided.

Fig. 4 shows a second embodiment of the invention particularly suitable for controlling a so-called rate response pacemaker. In this type of pacemaker the pacing rate depends upon metabolic needs, i.e. workload, as measured by a sensor. However for some heart disorders a high pacing rate can result in severe inconvenience or even danger to the patient.

The same reference numerals have been used in Fig. 4 for the same features already described with reference to Fig. 3. In this embodiment the controller 5 monitors the pacing rate. When a predetermined maximum rate is reached a signal is sent from the controller to the calculator 8. On receipt of this signal the calculator 8 ceases to access the memory to establish the new SIV and uses the last stored value. Alternatively the controller itself can store the SIV and not accept an update from calculator 8 when the predetermined maximum pacing rate is reached.

The SIV can be used to control maximum pacing rate in such a rate responsive pacemaker. When working at the maximum pacing rate in DDD mode it may be difficult to measure SIV since an interval which is spontaneous is no longer present. In this case the last value of SIV measured before a certain predetermined pacing rate has been exceeded is used to determine the maximum pacing rate allowed.

In VVI mode the spontaneous interval variation may be measured when the pacemaker is inhibited and a value thereof stored. This value may then be used when the pacemaker is not inhibited.

For AAI pacing a measure of the AV-conduction interval variation may be used to generate a measure which corresponds to the SIV. The ventricular activity is detected as the far field signal. For an AV synchronous system (e.g. VDD) the sensing of AV interval is also possible and this may be used to produce a signal representative of the spontaneous interval.

In a third embodiment depicted in Fig. 4 the invention may be used as a diagnostic monitoring device. The SIV as measured by the monitoring device may, for example, be used as an indicator of heart insufficiency between follow-ups.

The monitoring device is shown in Fig. 5 in conjunction with a pacemaker, though the device may be used separately.

The same reference numerals are used in Fig. 5 for the same features as in the preceding figures. In this embodiment the calculator 8 is provided with a store 9. In the store 9, values of the SIV are stored at regular intervals. These intervals may be determined by the patient's doctor. The storing of SIV at regular intervals may also be effected with the control of the controller 5 by the calculator being set out of action.

The information may be stored such that it may be accessed by telemetry. The information may also be monitored automatically by the monitoring device. If the monitoring indicates a change in the heart condition of the patient this could be automatically indicated to the patient, for instance by an audible signal. The device is particularly, but not exclusively, useful in identifying and monitoring Ischaemia.

The extra store 9 may also be provided in the first and second embodiments of the invention.

Although the invention has been described with respect to a pacemaker and a monitoring device, it may also be used with a defibrillator.

Claims

5

1. An implantable stimulating device (1) for electrical stimulation of the heart, comprising a stimulus generator (4) for generating electrical stimuli and at least one connection lead (3A, 3B) for conducting said stimuli from said generator to the heart, characterised in that said implantable stimulating device further
10 comprises means (6, 7, 8) for measuring the variation about their mean of a plurality of time intervals, each time interval being representative of the spontaneous interval between successive intrinsic heart beats, and means (5) for controlling a control parameter of said stimulus generator in dependence on the value of said time interval variation.

15

2. A stimulating device according to claim 1, characterised in that said control parameter is controlled in dependence from the value of only said time interval variation.

20

3. A stimulating device according either of claims 1 or 2, characterised in that said stimulus generator generates pacing stimuli, and the control parameter is a pacing parameter.

25

4. A stimulating device according to claim 3, characterised in that said control parameter controls the hysteresis interval of said pacing stimuli.

5. A stimulating device according to claim 3, characterised in that said control parameter controls the maximum stimulation rate.

30

6. A stimulating device according any one of the preceding claims, characterised in that the measuring means comprises a detector (6) connected to the connection

lead (3A, 3B) which detects said time interval, a memory (7) connected to said detector for storing a predetermined number of the latest detected time intervals, and a calculator (8) for calculating and producing signals representative of the spontaneous interval variation, said calculator using said latest detected time intervals.

5

7. A stimulating device according to any one of the preceding claims, characterised in that said measuring means (6, 7, 8) calculates said time interval variation by determining the difference between the largest and smallest value of a predetermined number of time intervals.

10

8. A stimulating device according to any one of the preceding claims, characterised in that said measuring means (6, 7, 8) calculates said time interval variation by determining the variance of a predetermined number of said time intervals.

1/2

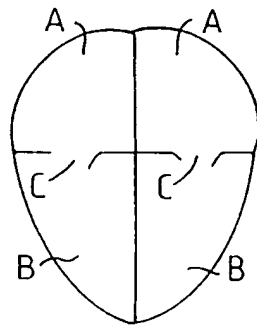


FIG. 1A

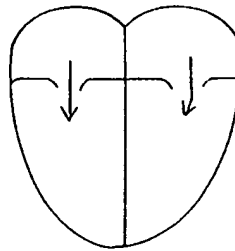


FIG. 1B

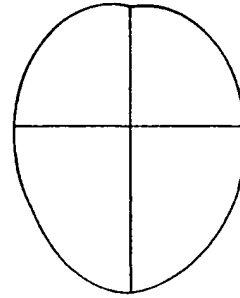


FIG. 1C

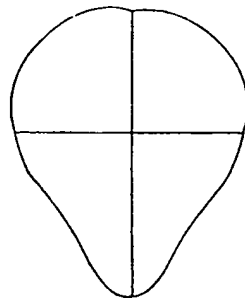


FIG. 1D

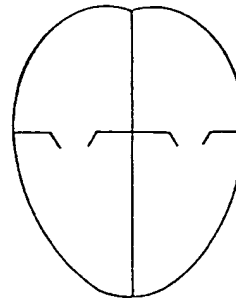
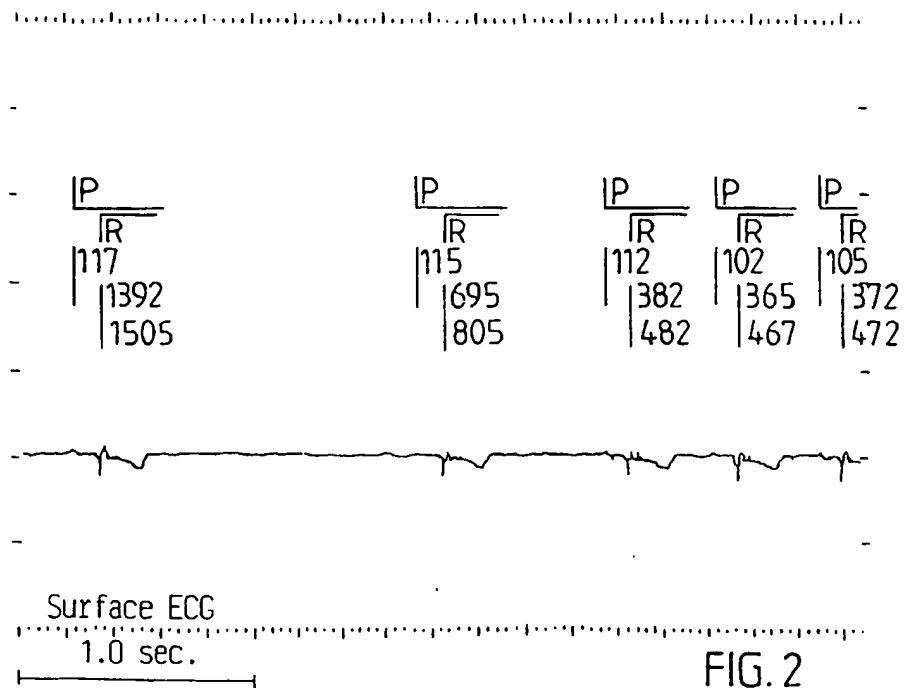
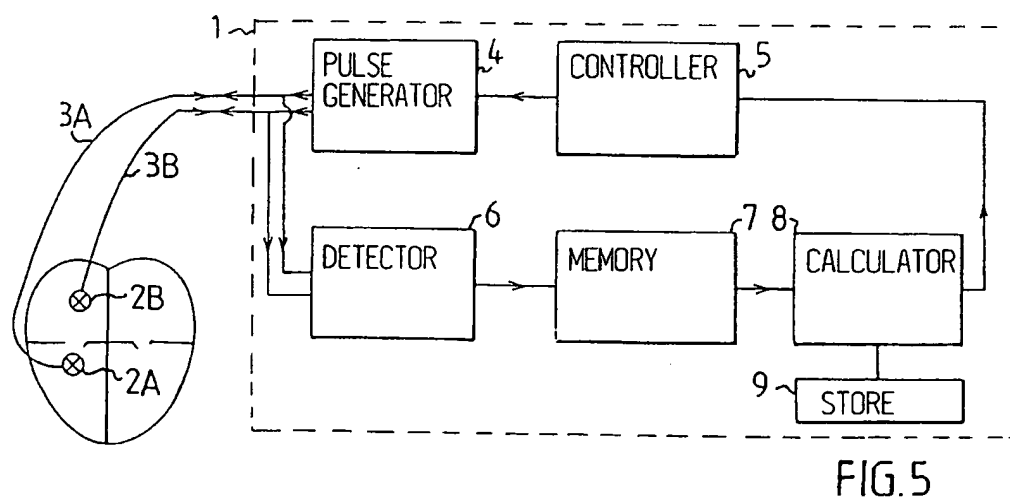
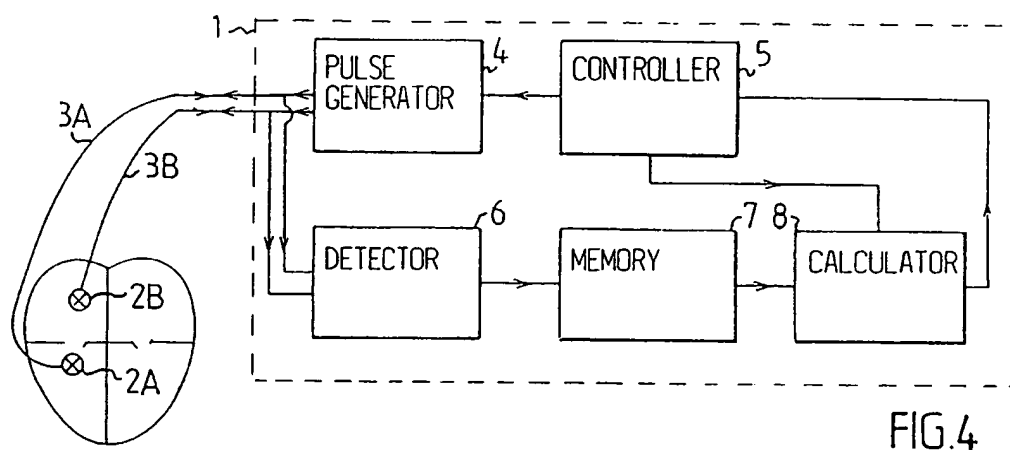
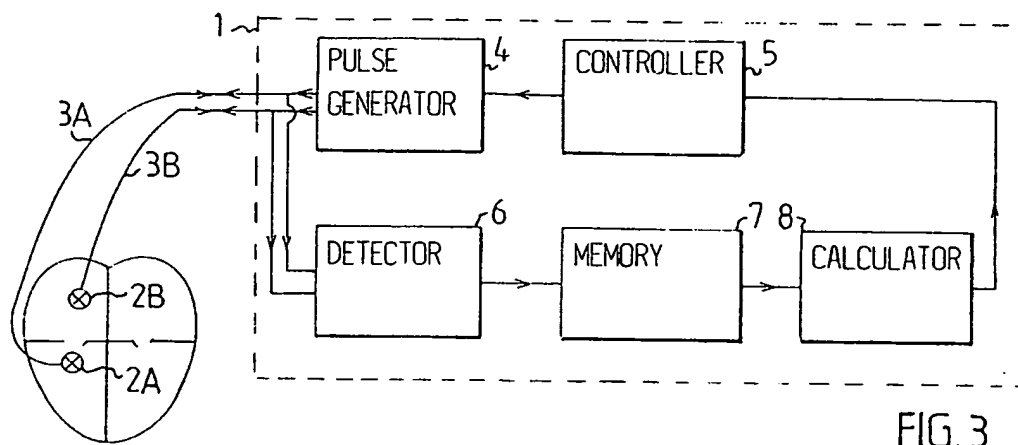


FIG. 1E



2/2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05443

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 358 303 A (MEDTRONIC INC) 14 March 1990	1-3,6
A	see the whole document ---	5,7,8
X	WO 93 16756 A (MEDTRONIC INC) 2 September 1993	1,3,4
A	see page 6, line 17 - page 9, line 5; figure 2A ---	2,5-8
A	"USE OF HEART RATE VARIABILITY TO DETECT VASOVAGAL SYNCOPE" RESEARCH DISCLOSURE, no. 380, 1 December 1995, page 820 XP000549836 ---	1-3
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 February 1998

Date of mailing of the international search report

16/02/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allen, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05443

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 91 03274 A (SIEMENS ELEMA AB ;SIEMENS AG (DE)) 21 March 1991 see page 4, line 15 - page 7, line 22; figures 1,4</p> <p>-----</p>	1-3,5-8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0358303 A	14-03-90	NONE	
WO 9316756 A	02-09-93	US 5284491 A AU 3433193 A	08-02-94 13-09-93
WO 9103274 A	21-03-91	AU 634981 B AU 4320189 A EP 0490892 A US 5253644 A	11-03-93 08-04-91 24-06-92 19-10-93

Form PCT/ISA/210 (patent family annex) (July 1992)